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Heart Rate Variability in the Diagnostics and CPAP Treatment of Obstructive Sleep Apnea

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Abstract

Obstructive sleep apnea (OSA) is the most common manifestation of sleep-related breathing disorders that are often accompanied by dysfunction of the autonomic nervous system. The main objective of the study was to assess the usefulness of heart rate variability (HRV) analysis in the diagnosis of patients with severe OSA and in the assessment of the effects of 3-month treatment with continuous positive airway pressure (CPAP). There were 54 patients enrolled in the study. The OSA group consisted of 39 patients suffering from severe OSA (apnea/hypopnea index >30/h), and the control group included 15 non-OSA patients with matched demographic characteristics and comorbidities. All patients underwent 24-h Holter electrocardiographic monitoring. HRV was analyzed using the time- and frequency-domains. We found that OSA patients had decreases in time-domains and increases in frequency-domains of HRV, compared to non-OSA controls, which strongly suggested a clinically disadvantageous shift in the balance of parasympathetic/sympathetic activity toward the latter. Further, CPAP treatment, partly, albeit significantly, reversed the OSA-induced changes in HRV. We conclude that HRV analysis may be of help in the diagnosis of OSA and in the monitoring of the effectiveness of treatment.

Keywords

Autonomic nervous system · Continuous positive airway pressure · Heart rate variability · Obstructive sleep apnea · Polysomnography

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1 Introduction

Obstructive sleep apnea (OSA) is a chronic disease and the most frequent type of sleep-related breathing disorders. It is characterized by obstruction of the upper airway despite ongoing breathing efforts. This most frequently leads to a fall in hemoglobin oxygen saturation and awakenings (AASM 2005). It is estimated that the syndrome is present in approximately 5% of the general human population (Jennum and Riha 2009; Pływaczewski et al. 2008). If untreated, OSA can lead to a number of severe medical conditions with a prevalence of cardiovascular episodes (Somers et al. 2008;

Marin et al. 2005). Polysomnography is the gold standard in the diagnosis of sleep breathing disorders, while the use of continuous positive airway pressure (CPAP) is the standard OSA treatment (Pataka and Riha 2013; Buchner et al. 2007).

The autonomic nervous system (ANS) plays a key role in the regulation of the physiological processes taking place during sleep. ANS activity is reflected in changes in arterial blood pressure, respiratory tract function, muscle tension, and heart rate variability (HRV). The HRV is defined as the variability of RR intervals measured electrocardiographically (ECG). It is affected by a number of factors, both physiological, e.g., breathing, physical, or psychological activity, and pathological such as diseases involving ANS dysfunction or medications. HRV analysis in time- and frequency-domains is a noninvasive tool for the evaluation of ANS activity. The time-domain provides the information on the RR interval length. The physiological heart beats generated in the sinus node are defined as normal (N) and the RR interval as normal-to-normal beats (NN). The commonly used time-domain parameters are the following: standard deviation of NN intervals (SDNN), standard deviation of the average NN intervals (SDANN), and the square root of the mean squared successive differences of NN intervals (RMSSD). A decrease in SDNN points to a possible loss of normal circadian variation in the length of NN intervals. This is observed in the condition of enhanced sympathetic activity. The RMSSD reflects the variability in the length of successive NN intervals, which is fundamentally affected by the vagal nerve parasympathetic activity (Reynolds et al. 2007; Bernardi et al. 2000; Malik and Camm 1993).

The frequency-domain of HRV assesses changes in the length of NN intervals in a given unit of time. The spectrum of NN interval frequency is obtained from the Fourier transformation method. The European Society of Cardiology recommends the spectral power analysis of NN intervals be made in the following frequency ranges: ultralow, lower than 0.0033 Hz (ULF); very low, 0.003–0.040 Hz (VLF); low, 0.04–0.15 Hz (LF); high, 0.15–0.40 Hz (HF); and total spectral power (TP). The spectral power in given frequency band provides the information on the cardiovascular modulation by specific components of ANS. Vagal nerve activity is represented by the HF band. The degree of both sympathetic and parasympathetic activity involved in the baroreceptor reflex mechanism is represented by LF band. Parasympathetic activity is represented by the ratio of LF to HF spectrum. The interpretation of ULF and VLF bands is somehow less clear. The VLF spectrum presumably reflects the parasympathetic activity, as it is inhibited by atropine and the ULF spectrum may reflect the circadian variations in HRV (Sun et al. 2011; ESC 1996).

There is ample evidence showing that the pathophysiological events occurring during sleep in OSA patients impair the ANS function (Xie et al. 2017; Tobaldini et al. 2013; Flevari et al. 2015; Karasulu et al. 2012; Stein and Pu 2012; Gula et al. 2003). Blood pressure variations in the chest cavity, changes in heart load, and apneic episodes and multiple awakenings at night tend to shift the vagosympathetic balance toward the latter component. A growing health issue of OSA, with the syndrome's socioeconomic implications, calls for a further exploration of the pathophysiological mechanisms involved. Polysomnography remains a highly specialized diagnostic procedure, with a rather limited general accessibility. Therefore, other effective OSA screening and diagnostic tools are searched for. The HRV analysis, based on ECG Holter monitoring, has been proposed as such a tool (Gong et al. 2016; Harrington et al. 2013; Hayano et al. 2013; Roche et al. 1999b). Therefore, the present study seeks to define to what extent the HRV analysis could be useful in the diagnosis of OSA and in the assessment of CPAP treatment efficacy.

2 Methods

2.1 Patients, Clinical Tests, and Study Protocol

There were two groups of patients in this study: 39 (29 men and 10 women) middle-aged OSA patients, who manifested severe symptoms of the

disease (AHI ≥30 episodes/h), and 15 control patients (10 men and 5 women) free of any sleep-related breathing disorders. Both groups of patients were matched regarding the age, gender, and a history of hypertension. The BMI was considerably higher in the OSA patients (Table 1). The OSA patients qualified for the study were chosen from the initial cohort of 140 patients who were at onset considered as the potential candidates for the study. The qualification and exclusion criteria for the study are listed in Table 2. All patients underwent the baseline evaluation consisting of medical examination and measurement of blood pressure, blood oxygen saturation, body mass index (BMI), ECG, sleepiness on the Epworth sleepiness scale (ESS), basic blood tests (morphology; glucose level; lipids; sodium, potassium, and magnesium levels; creatinine; N-terminal pro b-type natriuretic peptide (NT-proBNP); alanine transaminase; bilirubin; total protein; C-reactive protein; and thyrotropin-stimulating hormone), spirometry, and a chest X-ray.

Polysomnography and 24-h ECG Holter monitoring were conducted in all the subjects. In the group of OSA patients, CPAP treatment was initiated. Therapeutic CPAP pressure values were defined during a parallel polysomnography (CPAP titration). The control group was not subject to the treatment. The OSA group was re-examined after 3-month CPAP treatment (Visit 2). The study protocol is presented in Fig. 1. A 12-channel polysomnography was conducted according to the American Academy of Sleep Medicine (AASM) guidelines (AASM 2005), using a SOMNOlab 2 device (Weinmann Emergency Medical Technology, Hamburg, Germany). The following variables were used in the final analysis: number of apneas and hypopneas per hour of sleep, apnea/hypopnea index (AHI), average and minimum arterial oxygen saturation, and overall desaturation index, i.e., the number of desaturations per hour of sleep (ODI). The ESS was used to assess daily sleepiness. Therapeutic CPAP pressure (i.e., the minimum pressure value generated by the device to maintain unobstructed airway) was defined in the process of CPAP titration with the use of an auto-CPAP device (REMStar; Philips Respironics, Murrysville, PA) under polysomnographic control. The effective duration of CPAP home therapy was assessed on the basis of data collected from CPAP device memory cards and analyzed with EncorePRO software (Philips Respironics, Murrysville, PA).

Table 1 Baseline characteristics of the obstructive sleep apnea (OSA) and control patients

Parameter		Controls	OSA patients
Age (years)		55.2 ± 2.7	54.4 ± 3.0
BMI (kg/m^2)		31.7 ± 1.2	33.9 ± 2.4∗
Gender	Male, *n* (%)	10 (66.7)	29 (74.4)
	Female, *n* (%)	5 (33.3)	10 (25.6)
Hypertension, n (%)		11 (73.3)	35 (89.7)

Data are means ±SD and number (%) of subjects. *BMI* body mass index; ∗$p < 0.001$ between the two groups

2.2 Evaluation of Heart Rate Variability (HRV)

HRV evaluation was made on the basis of ECG wave obtained from a full 24-h Holter recording of high quality, performed with a 3-channel monitor (Aspel; HolCARD 24 W, Zabierzów, Poland), according to the clinical practice guidelines of the European Society of Cardiology (ESC 1996). The following parameters were analyzed in the time-domain: SDNN, SDANN in consecutive 5-min intervals, and RMSSD. The spectral power of HRV was analyzed in the following frequency bands: ULF, VLF, LF, and HF.

2.3 Statistical Elaboration

Data were expressed as means ±SD or medians with minimum-maximum values. Since the intragroup results had a skewed distribution, the Mann-Whitney U test was used for comparisons. Comparisons between the study and control groups were made with a *t*-test for quantitative variables and a Chi-squared test for qualitative variable. The analysis of changes between visits in the OSA group was done with the Wilcoxon signed-rank test for repeated measurements. The

Table 2 Inclusion and exclusion criteria, comorbilities and pharmacotherapy

Inclusion criteria
Age > 18 years
Severe OSA (AHI ≥ 30/h)
ESS score > 10 points
Confirmed CPAP efficacy (AHI <10/h)
Exclusion criteria
Age < 18 years
AHI < 30/h
Low-quality ECG Holter
Comorbidities
Central/mixed sleep apnea
Heart failure
Ischemic heart disease
History of myocardial infarction
Persistent atrial fibrillation
History of cardioversion or ablation
History of stroke
Renal insufficiency
Liver insufficiency
Diabetes
Neoplasm
Pharmacotherapy
Beta-blockers
Calcium blockers
Digoxin, ivabradine

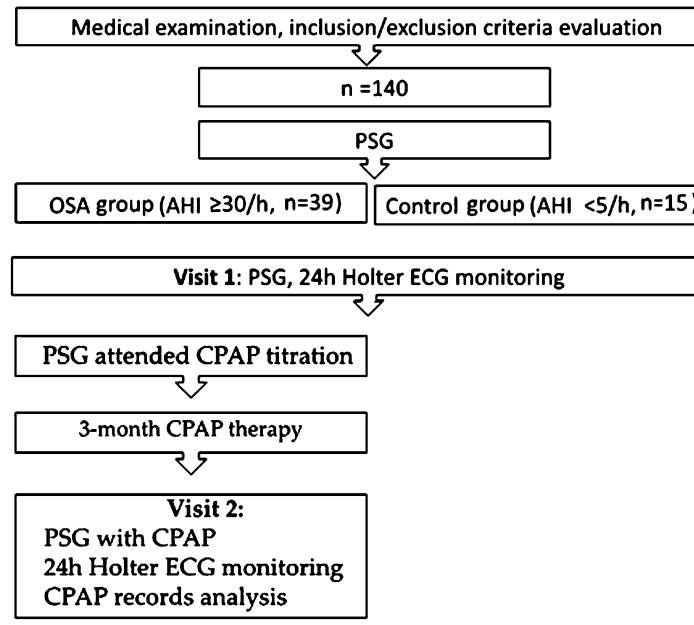

Fig. 1 Scheme of study paradigm

Table 3 Heart rate variability parameters in controls and in obstructive sleep apnea (OSA) patients at baseline (Visit 1) and in OSA patients after 3-month CPAP treatment (Visit 2)

	Controls	OSA patients	
Parameter	Visit 1		Visit 2
ESS (points)	5 (0–8)	15 (11–18) ∗	5 (1–9) ǂ
AHI (episodes per hour)	2.5 (0–4.7)	51 (31–85) ∗	4 (0–8) ǂ!
ODI (episodes per hour)	2 (0–3.6)	49 (25–87) ∗	26 (0–5.2) ǂ!
Average nocturnal SaO_2 (%)	96 (94–97)	91 (81–95) ∗	95 (94–97) ǂ
Min. SaO_2 (%)	90 (87–92)	75 (50–86) ∗	87 (83–90) ǂ !!
SDNN (ms)	138 (115–161)	114 (76–166) †	143 (83–176) ǂ
SDANN (ms)	124 (110–141)	99 (53–132) ∗	123 (70–212) ǂ
RMSSD (ms)	32 (29–37)	32 (23–37)	37 (25–43) ǂ !!
ULF (ms^2)	119 (115–124)	141 (128–176) ∗	128 (112–160) ǂ !!
VLF (ms^2)	519 (507–531)	631 (553–773) ∗	561 (516–694) ǂ !!
LF (ms^2)	416 (231–431)	476 (435–565) ∗	439 (401–497) ǂ !!
HF (ms^2)	351 (339–361)	311 (286–339) ∗	329 (245–391) ǂ !!
TP (ms^2)	1,405 (1,214–1,431)	1,557 (1,453–1,776) ∗	1,472 (1,325–1,626) ǂ !!
LF/HF	1.18 (0.66–1.24)	1.55 (1.29–1.78) ∗	1.37 (1.09–1.73) ǂ !!

Data are means ±SD, medians (min-max), and number of episodes
ESS Epworth sleepiness scale, *AHI* apnea/hypopnea index, *ODI* desaturations per hour of sleep, *SaO_2* arterial oxygen saturation, *SDNN* standard deviation of NN intervals, *SDANN* standard deviation of the average NN intervals, *RMSSD* square root of the mean squared successive differences of NN intervals, *ULF* ultralow frequency < 0.0033 Hz, *VLF* very low frequency 0.003–0.040 Hz, *LF* low frequency 0.04–0.15, *HF* high frequency 0.15–0.40 Hz, *TP* total spectral power ∗ $p < 0.001$ and † $p = 0.003$ between Visit 1 patients vs. control subjects; ǂ $p < 0.001$ between Visit 2 vs. Visit 1 same patients; ! $p < 0.05$ and !! $p < 0.001$ between Visit 2 patients vs. controls

associations among variables were assessed with a multivariate analysis of linear regression. The statistical significance level was set at $\alpha = 0.05$. The analyses were conducted with the R-3.0.2 project for statistical computing (R Foundation for Statistical Computing; Vienna, Austria).

3 Results

The SDNN, SDANN, and HF spectral power values were significantly lower in the OSA group. On the other side, ULF, VLF, LF, TP, and the LF/HF ratio of spectral power values were all significantly greater in the OSA patients than those in the control subjects. The number of ODI was manifold greater in the OSA patients than in controls (Table 3). The increases in ODI in the OSA patients were associated with significantly higher VLF, LF, TP, and the LF/HF spectral power ratio (Table 4). The evaluation of these associations was controlled for age, gender, body mass index (BMI), systolic (SBP) and diastolic (DBP) blood pressure, and a history of hypertension. There were no other associations among the OSA characteristics and frequency- or time-domain spectral data.

Three-month CPAP treatment resulted in significant increases in SDNN, SDANNN, RMSSD, and the HF spectral power, while the ULF, VLF, LF, TP bands, and the LF/HF ratio all decreased in OSA patients. The increases in SDNN and SDANN after treatment reached the level present in controls. On the other side, ULF, VLF, LF, TP bands, and the LF/HF, despite the decreases, remained at a level significantly higher than those in controls (Table 3).

4 Discussion

OSA patients manifest ANS dysfunction resulting from the pathophysiological events related to recurring episodes of apnea, hypoxia, and awakenings (Stein and Pu 2012; Somers et al. 1995). The ANS dysfunction is present not only during sleep but also during daytime (Narkiewicz and Somers 2001; Carlson et al. 1996). The ANS

Table 4 Associations between the increase in the number of desaturations per hour of sleep (ODI) and the spectral power frequency bands of heart rate variability in OSA patients

ODI	*r*	SE	*p*
VLF (ms^2)	2.074	0.953	0.038
LF (ms^2)	1.551	0.584	0.013
TP (ms^2)	3.629	1.272	0.008
LF/HF	0.007	0.003	0.018

r regression coefficient, *SE* standard error, *VLF* very low frequency 0.003–0.040 Hz, *LF* low frequency 0.04–0.15, *TP* total spectral power

dysfunction in OSA not only is a syndrome's manifestation but is at play in the development of cardiovascular complications. Attempts have been made to define OSA-related HRV changes, assessed by way of ECG Holter monitoring, as a screening tool. Although promising, the results of those studies have not yet defined the exact role of ECG Holter monitoring in the diagnostics of OSA (Gong et al. 2016; Harrington et al. 2013; Hayano et al. 2013; Sun et al. 2011; Roche et al. 1999b). Therefore, the goal of the present study was to reevaluate HRV changes in a group of fairly homogenous OSA patients in terms of disease severity, comorbidities, and therapy. We found significantly lower values of SDNN and SDANN in severe OSA, compared to control subjects. These results point to a lower parasympathetic activity, which conforms with a shift in ANS balance toward the sympathetic side. Our results are in line with those of Narkiewicz and Somers (2001), who have shown increased muscle sympathetic nerve activity in OSA, both during sleep and wakefulness. Those authors suggested that increased sympathetic tone could be related to altered baroreceptor reflex, which has been further confirmed by Carlson et al. (1996). In the present study, patients with the highest AHI had the lowest SDNN, the corollary of which is patients with severe OSA had a low level of advantageous, particularly from the standpoint of cardiovascular function, parasympathetic activity. Along the same line of evidence, Aydin et al. (2004) and Véber et al. (2014) have shown a significant decrease in time-domain of HVR in OSA. On the other hand, Karasulu et al. (2012) have reported the opposite tendency in a study in 30 OSA patients of differing disease severity and comorbidities, which in addition was not based on 24-h ECG recordings. There are also studies that fail to show the presence of any appreciable differences in the time-domain of HRV between OSA patients and healthy subjects (Lado et al. 2012; Zhu et al. 2012). In this regard, it is worth noting that in the present study, the medians of time-domain parameters in severe OSA, although significantly lower than those in non-OSA controls, still met the limit of normal values suggested in the guidelines (ESC 1996). Thus, we presume that the usefulness of time-domain analysis of HRV in the diagnostics of severe OSA remains unsettled.

In this study, we also showed that patients with severe OSA had a significant decrease in HF spectral power with simultaneous increases in LF, VLF, ULF, and the overall TP value. A low HF, compared to control subjects, points to a decrease in parasympathetic activity, the reasoning further confirmed by an increase in the LF/HF ratio. A counterincrease in sympathetic activity might thus be presumed. We further showed that an increase in ODI was related to the increases in LF spectral power and LF/HF ratio. Hypoxia, expressed in the ODI values, may add to the stimulation of sympathetic activity through the chemoreceptor reflex (Narkiewicz and Somers 2001; Somers et al. 1995), and it increases the VLF spectral power, which we also noticed. The VLF spectrum presumably represents the exaggerated heart rate oscillations, caused by recurring episodes of apnea during sleep, in a short time span of 1–5 min. An increase in VLF, noticed also in other studies (Karasulu et al. 2012; Aydin et al. 2004; Gula et al. 2003), has been proposed a marker of OSA (Malik and Camm 1993).

Palma et al. (2014) have described two basic phenotypes of OSA syndrome: with and without hypoxia, examining a group of 129 patients with severe OSA. The hypoxic phenotype is characterized by an increase in sympathetic activity, expressed as increases in both LF spectral power and LF/HF ratio, compared to the non-hypoxic OSA or healthy subjects. The presence of two OSA phenotypes, distinguished by the severity of hypoxia and relating the ANS

disorders to the hypoxic phenotype, but having a similar AHI, is an interesting clinical concept as it would enable a prompt association of cardiovascular risk with hypoxia. However, the use of frequency-domain of HRV as a diagnostic tool for OSA also is limited by a wide range of normal spectral power values for the respective frequencies. Nonetheless, the present study showed that increased spectral power of LF and VF, with a concurrent fall in HF, would point to severe OSA. Likewise, the LF/HF ratio exceeding 2.5 might suggest increased sympathetic activity, which could suggest the diagnosis of OSA. Changes in the frequency-domain of HRV we noticed in this study are in line with the notion that hypoxia is a key factor linking severe OSA with altered ANS activity.

We also showed that CPAP treatment led to distinct increases in all time-domain parameters of HRV. Concerning the frequency-domain, HF spectral power increased, with concurrent decreases in ULF, VLF, LF, and LF/HF ratio. A significant decrease in TP also was noticed. Such changes may be considered as reflecting a clinically favorable shift back to parasympathetic edge over sympathetic modulation as a result of CPAP treatment. There are rather scarce studies evaluating the influence of CPAP on HRV. Roche et al. (1999a) have evaluated the effects of 3-month CPAP treatment on the time- and frequency-domains of HRV in severe OSA (14 patients; average AHI = 50.6/h), based on a 24-h ECG recordings. The authors notice an increasing tendency in the time-domain parameters, and distinct increases in HF, with concurrent decreases in LF and VLF spectral power. Chrysostomakis et al. (2006) have evaluated the effects of 2-month CPAP treatment on the time-domain of HVR in 31 patients with moderate and severe OSA. The authors also notice an increasing tendency for SDNN and SDANN. Limphanudom et al. (2007) have evaluated the effects of 6-month CPAP treatment on the time- and frequency-domains of HRV in a small group of ten patients with severe OSA. These authors failed to notice any appreciable differences before and after therapy.

In summary, in comparison to healthy subjects, patients with severe OSA have decreases in time-domains and increases in frequency-domains of HRV which are strongly suggestive of a disadvantageous, from the clinical standpoint, shift in the balance of parasympathetic/sympathetic activity toward the latter. CPAP treatment significantly, albeit not entirely, reversed these changes. These findings show that HVR analysis, based on an easily accessible 24-h ECG Holter monitoring, may help identify the presence of OSA and the effectiveness of CPAP treatment, which makes it a potentially valuable clinical tool. Nonetheless, the usefulness of the HRV evaluation is limited by all too often comorbidities accompanying OSA and by their pharmacotherapy, which may affect the HVR.

Conflicts of Interest The authors declare no conflicts of interest in relation to this article.

Ethical Approval The project was approved by the Bioethics Committee of the Jagiellonian University in Cracow, Poland (permit KBET/115/B/2010). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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